REMARKS

Claims 1-12, 14, 18, and 21 are pending in the application. Claims 1, 3, and 10 have been amended.

To address the objection and rejection of claims 3 and 10, claim 1 has been amended to eliminate a specific range for the first and second concentrations of Mg. Rather, claim 1 now requires that both ranges be unphysiologically high in Mg concentration. As explained in paragraph [0041], it was found that the use of unphysiologically high extracellular concentrations of magnesium allows for the generation of chondrons and that increasing the extracellular magnesium concentration at least once allows for differentiation. Paragraphs [0042] and [0043] provide exemplary ranges for Mg for the first and second cultivations. Claim 3 is amended to use the range specified in paragraph [0044] for the second cultivation at increased Mg concentration. Claim 10 has been amended to simply eliminate the range. Paragraph [0031] defines unphysiologically high extracellular concentration of Mg as being a concentration that is above that which is in the body that the cells are derived from, and specifically provides a concentration for humans.

As discussed in the previous amendment, an important and distinguishing feature of the invention is based on the discovery that different stages of chondrocyte cultivation can be controlled by having a a first stage of cell cultivation at an unphysiologically high extracellular concentration of magnesium and, then at least one subsequent stage of cultivation during which the concentration of Mg is increased to an even higher level of unphysiologically high extracellular magnesium concentration. The first stage is a proliferation stage, and the second stage is a differentiation stage. The Example section on page 14 of the application specifically references proliferation and differentiation. Paragraphs [0043] and [0044] specification describe increasing the magnesium concentration at least once during cultivation, and the use of unphysiologically high levels of magnesium during both the first and second stages.

Claim 1 has been re-formulated to highlight this two step process. That is, claim 1 now clear addresses the two step elevation of the magnesium concentration by identifying cultivation of chondrocytes at a first unphysiologically high extracellular concentration of magnesium and, thereafter, cultivation of the chondrocytes at a second unphysiologically high extracellular concentration of magnesium that is increased over the first unphysiologically high extracellular concentration. Moreover, claim 1 clarifies that increasing the concentration

from the first to the second unphysiologically high extracellular concentration of magnesium shifts the chondrocytes from proliferation to differentiation. This amendment specifically includes in claim 1 the proliferation and differentiation phases, as noted by the Examiner on page 8 of the office action, and as specifically described in the Example section on page 14 of the application.

Claims 1, 2, 5, and 7-9 are rejected as being obvious over U.S. Patent 4,978,661 to Caruso in view of Egerbacher (Vet Pathol 38:143-148, 2001). Claims 1, 2, 4-9, 11, 12, 14, 18 and 21 have been rejected as being obvious over U.S. Patent Publication 2001/0012965 to Masuda in view of Egerbacher, U.S. Patent 6,841,150 to Halvorsen, and U.S. Patent Publication 2005/0139040 to Lindenberg. These rejections are traversed in view of the amendments above.

At the outset, none of the references describe changing concentration of magnesium ions in a way that at a first unphysiologically high concentration proliferation occurs, and at a second unphysiologically high concentration which is higher than the first concentration differentiation of the chondrocytes is achieved. That is, only the applicant has shown and described a process where two different elevated levels of magnsium ions are used, and where the cultivation moves from proliferation to differentiation by moving from a first elevated level of Mg to a second, higher, elevated level of Mg.

Since no reference show or suggest two different, unphysiologically high levels of Mg, and no reference contemplates cultivation of chondrocytes in a manner which achieves proliferation then differentiation based on an increase in the elevated level of Mg, the claims are not obvious over any combination of references of record.

Moreover, Caruso is not relevant for chondrocytes. Rather, it describes treatment of patients suffering from rheumatoid arthritis using 6-halo-4-quinolone. Caruso does not provide one of ordinary skill in the art with any reference point for proliferation and differentiation of chondrocytes.

Masuda describes a process for the in vitro production of transplantable cartilage tissue (see title). As acknowledged in the office action, Masuda does not show or describe culturing chondrocytes in unphysiologically high concentrations of Mg. It also does not describe use two different unphysiologically high concentrations of Mg in different culturing steps to achieve proliferation then differentiation. Neither Halvorsen nor Lindenberg make up for this deficiency.

Egerbacher, which has been discussed at length in the prosecution of this case and

relates to the effect of magnesium in quinolone treatment. Egerbacher emphasizes that quinolone has a chondrotoxic effect (Egerbacher states "Chondrocytes cultivated in the presence of quinolones and Mg-free medium show sever alterations in cytoskeleton and decreased ability to adhere to the culture dish...quinolone effects on cell proliferation seem to be an independent process that is not influenced by magnesium supplementation"). One of ordinary skill in the art would not combine the teachings of Caruso and Egerbacher as suggested in the office action. This is because Egerbacher teaches chondrotoxic effects of the quinolones disclosed in Caruso. (Egerbacher states "These results suggest that a great part of quinolone induced damage is due to magnesium complex formation, as Mg2+ supplementation is able to reduce the effects in vitro"). Moreover, the Egerbacher abstract teaches that addition of Mg ions did not increase the rate of cell proliferation.

That is, Egerbacher clearly does not teach that at an unphysiologically high concentration chondrocyte proliferation occurs, and at a second concentration of Mg that is higher than the first concentration, differentiation is achieved. This concept is also not taught in any of Carusa, Masuda, Halvorsen, or Lindenberg.

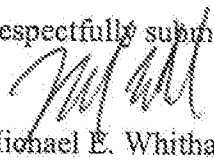
In view of the above, it is respectfully requested that the application be reconsidered, that claims 1-12, 14, 18 and 21 be allowed, and that the application be passed to issue.

With respect to the applicants claim of priority, it is noted that the provisional application and European application do describe using unphysiologically high concentrations of Mg (specifically in the provisional application it is noted on page 6, line 12 that elevating the extracellular magnesium concentration above physiologic levels leads to enhanced tissue generation; see also lines 35-38 on page 6 and lines 1-5 on page 7 and lines 8-16 on page 9 as well as claims 8, 9 and 17 in the provisional application) and promoting specific stages of chondrocyte maturation using magnesium (see page 7, lines 7-10 of the U.S. provisional; see also line 18 on page 7)

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary in a telephonic or personal interview.

A provisional petition is hereby made for any extension of time necessary for the continued pendency during the life of this application. Please charge any fees for such provisional petition and any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,



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